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di Studi di Medicina Trasfusionale
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SIMTI

CAR-T e Mieloma Multiplo

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Disclosures Roberto Mina

Research Support/P.I.	
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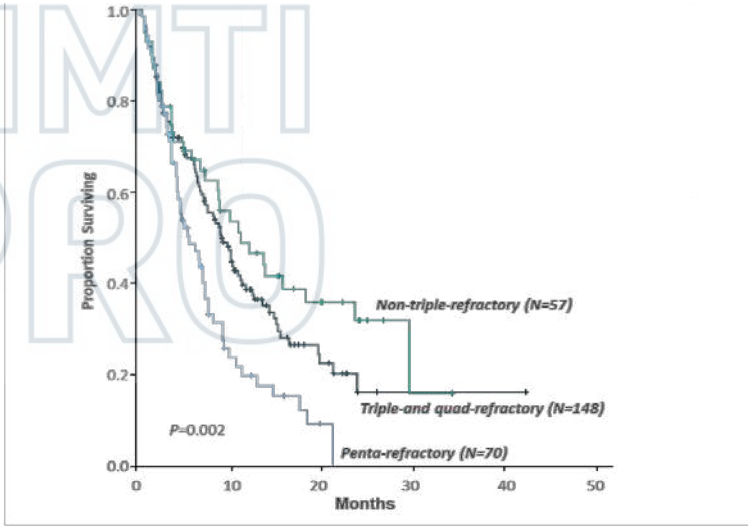
Triple-class/penta-refractory MM a new unmet clinical need

MAMMOTH STUDY[1]	ORR	Median PFS	Median OS
Triple class refractory (1 PI, 1 IMiD, anti CD-38)	30%	3.4 months	9.2 months
Penta refractory(2 PIs, 2 IMiDs, anti CD-38)	<30%	NR	5.6 months

TREATMENT OPTIONS:

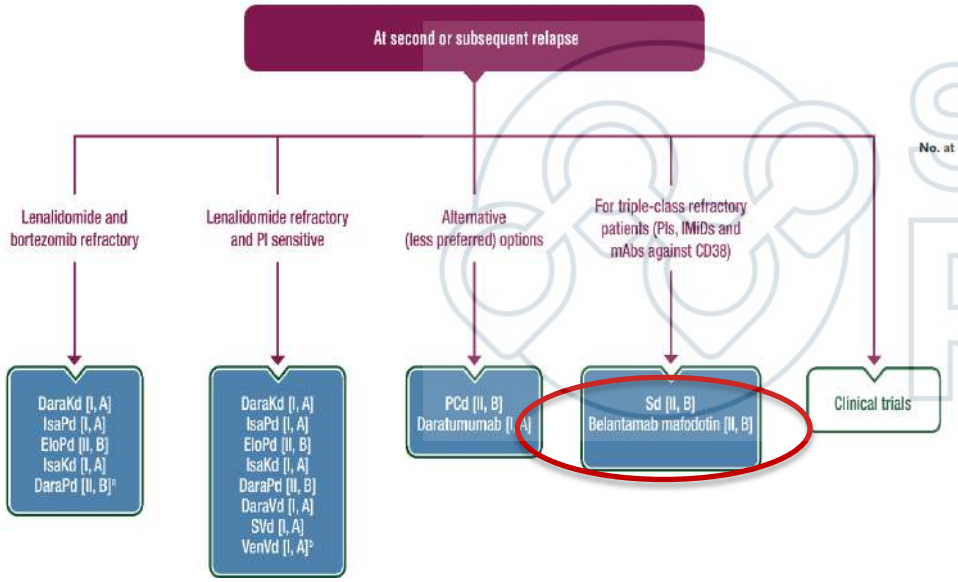
1. **Trial participation not possible (non available, non-secretory disease, poor marrow function, CKD, aggressive PD)**
   - **Retreatment** with drugs used in prior lines
   - Use of recently approved **drugs with novel mode of action**
     - **Belantamab mafodotin** (FDA/EMA approved)[2-3]
     - **Selinexor** (FDA/EMA approved)[4-5]
     - **Melphalan flufenamide**? Pending EMA/FDA on held, possibility of NPP in Italy[6]
     - **Ide-cel** (FDA/EMA approved)[7-8]
     - **Cilta-cel** (FDA approved)[9]



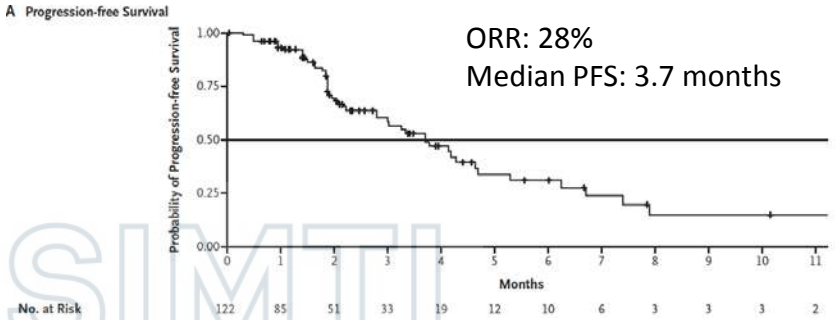
IMiD, immunomodulatory drug; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor

1. Gandhi UH et al. Leukemia 2019; 33(9):2266-2275; 2. FDA https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma; 3. EMA: https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep; 4. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selinexor-refractory-or-relapsed-multiple-myeloma; 5. https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio; 6. Mina R. Personal communication; 7. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-idecabtagene-vicleucel-multiple-myeloma; 8. https://www.ema.europa.eu/en/news/first-cell-based-gene-therapy-treat-adult-patients-multiple-myeloma; 9. https://www.jnj.com/u-s-fda-approves-carvykti-ciltacabtagene-autoleucel-janssens-first-cell-therapy-a-bcma-directed-car-t-immunotherapy-for-the-treatment-of-patients-with-relapsed-or-refractory-multiple-myeloma

2021 ESMO guidelines for RRMM: treatment options for triple class refractory multiple myeloma

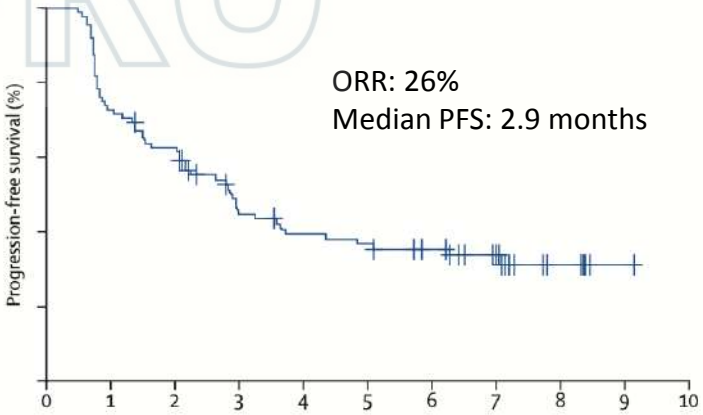


Selinexor-dexamethasone



ORR: 28%
Median PFS: 3.7 months

Belantamab-mafodotin



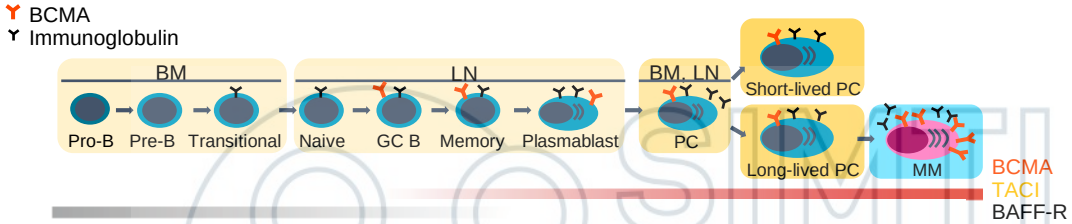
ORR: 26%
Median PFS: 2.9 months

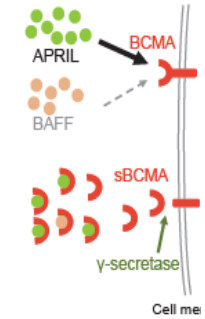
C, cyclophosphamide; D, dexamethasone; d, low dose dexamethasone; Dara, daratumumab; Elo, elotuzumab; IMiDs, immunomodulatory drug; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; mAb, monoclonal antibody; Pano, panobinostat; P, pomalidomide; PI, proteasome inhibitor; R, lenalidomide; S, Selinexor; V, bortezomib; Ven, venetoclax

Dimopoulos et al. Ann Oncol 2021;32(3):309-22; Chari A et al, NEJM 2019; Lonial et al. Lancet oncol 2019.

Targeting BCMA

(B Cell Maturation Antigen)



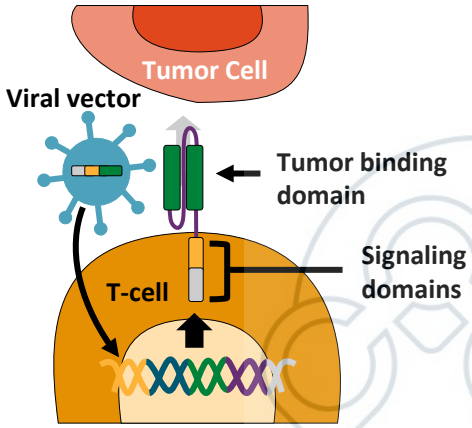


- BCMA is an antigen expressed specifically on PCs and myeloma cells
  - Member of TNFR superfamily. Binds 2 ligands (BAFF e APRIL)
  - higher expression in myeloma cells than normal PCs
  - key role in B-cell maturation and differentiation
  - promotes myeloma cell growth, chemoresistance, and immunosuppression in the BM microenvironment
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma

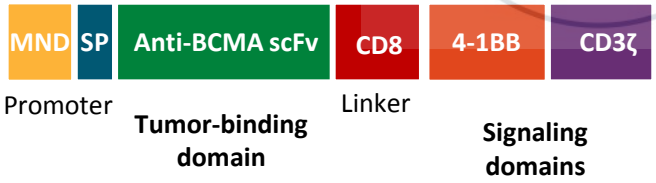
APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; GC, germinal centre; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

Cho SF, et al. Front Immunol. 2018;9:1821. Moreaux J, et al. Blood. 2004;103:3148-57. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

Idecabtagene Vicleucel (ide-cel; bb2121): anti-BCMA CAR T-Cell Construct Design

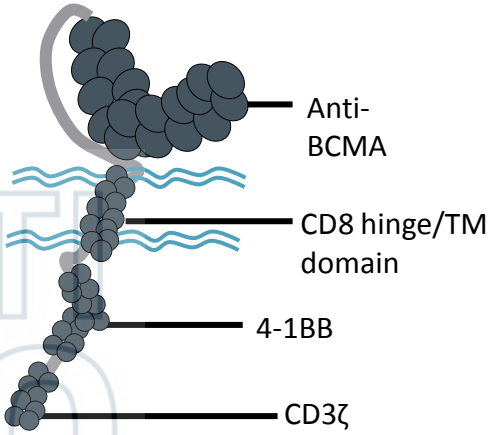


Idecabtagene CAR design



Extracellular domain
Targeting domain
Hinge/TM domain

Intracellular domain
Costimulatory domain
T-cell activation domain



Idecabtagene: second-generation CAR construct

- **Autologous** T-cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: **Anti-BCMA**
- Costimulatory domain: **4-1BB**
- T-cell activation domain: **CD3ζ**

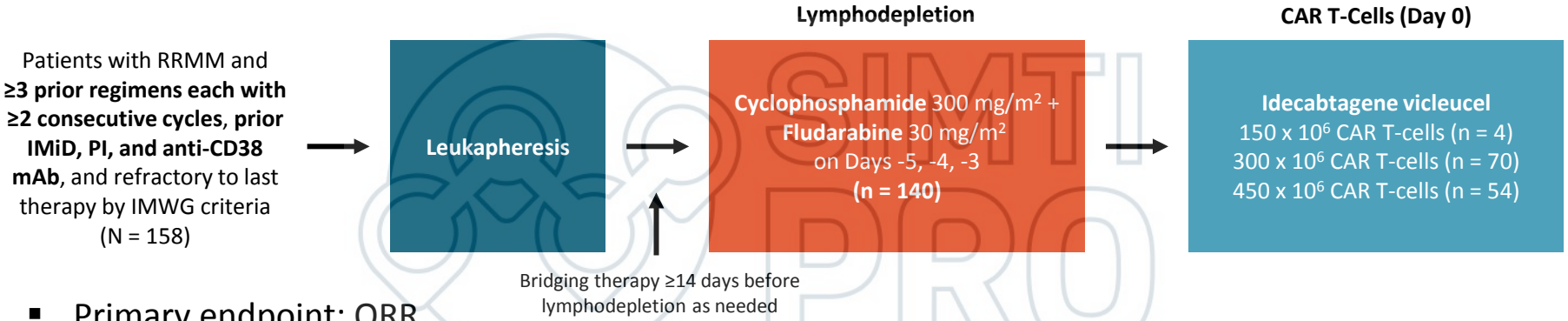
4-1BB associated with less toxicity and more durable CAR T-cell persistence than CD28 costimulatory domain

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; MND, dl587 rev primer-binding site substituted; scFv, short chain variable fragment; SP, signaling peptide; TM, transmembrane domain.

1. Raje N et al, *N Engl J Med* 2019;380:1726–37. **2.** Raje N, et al. ASCO 2018. Abstract. 8007.

KarMMa: Idecabtagene Vicleucel for RRMM

- Multicenter, single-arm phase II trial



- Primary endpoint: ORR
- Secondary endpoints: CR (key), DoR, PFS, OS, MRD, safety, PK, QoL, and HEOR
- Exploratory endpoints: immunogenicity, BCMA expression/loss, cytokines, T-cell immunophenotype, and GEP in BM

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; DoR, duration of response; HEOR, health economics and outcomes research; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; mAb, monoclonal antibody; MRD, measurable residual disease; ORR, overall response rate, OS, overall survival; PI, proteasome inhibitor; PFS, progression-free response; PK, pharmacokinetic; QoL, Quality of life; RRMM, relapsed/refractory multiple myeloma; TTR, time to response.

1. Munshi N, et al. ASCO 2020. Abstract 8503., NEJM 2021

KarMMa: Baseline Characteristics

Characteristic	Ide-cel Treated (N = 128)
Median age, years (range)	61 (33–78)
Male, %	59
ECOG PS, % ▪ 0 ▪ 1 ▪ 2	 45 53 2
R-ISS stage, % ▪ I ▪ II ▪ III	 11 70 16
High-risk cytogenetics (del[17p], t[4;14], t[14;16]), %	35
High tumor burden (≥ 50% BMPCs), %	51

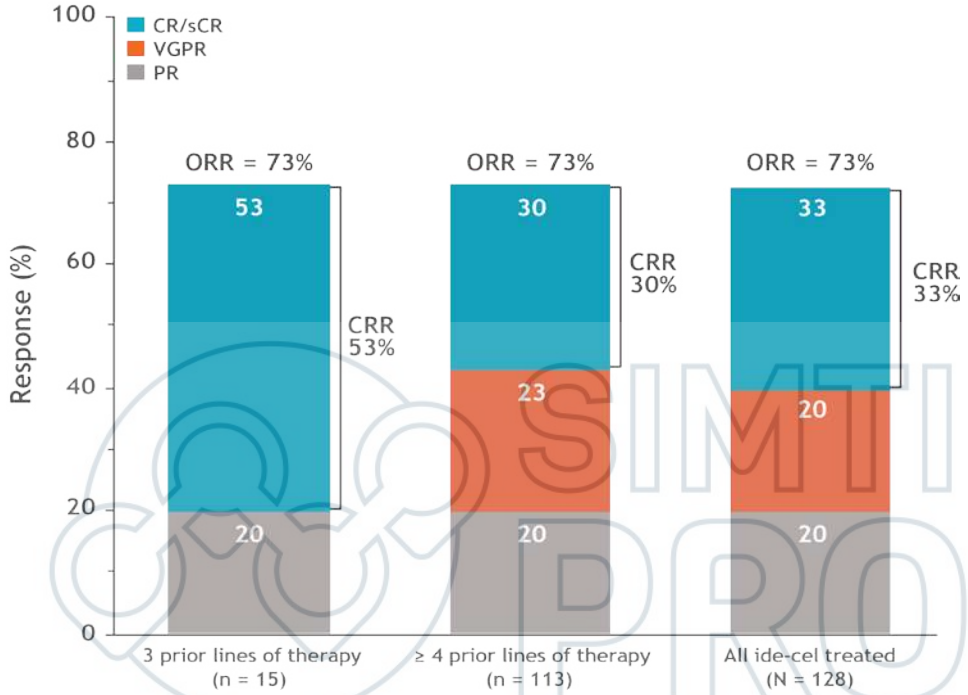
88% of patients received bridging therapy; only 4% responded

Characteristic	Ide-cel Treated (N = 128)
Tumor BCMA expression (≥ 50% BCMA positive), %	85
Extramedullary disease, %	39
Median time since initial diagnosis, years (range)	6 (1–18)
Median no. of prior anti-MM regimens (range)	6 (3–16)
Prior autologous SCT, % ▪ 1 ▪ >1	 94 34
Any bridging therapies for MM, %	88
Refractory status, % ▪ Anti-CD38 mAb refractory ▪ Triple refractory	 94 84

BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; ECOG PS, Eastern Cooperative Oncology Group performance score; ida-cel, idecabtagene vicleucel; mAb, monoclonal antibody; MM, multiple myeloma; SCT, stem cell transplant.

1. Munshi N, et al. ASCO 2020. Abstract 8503.

Best overall response by number of prior lines of therapy and in all patients

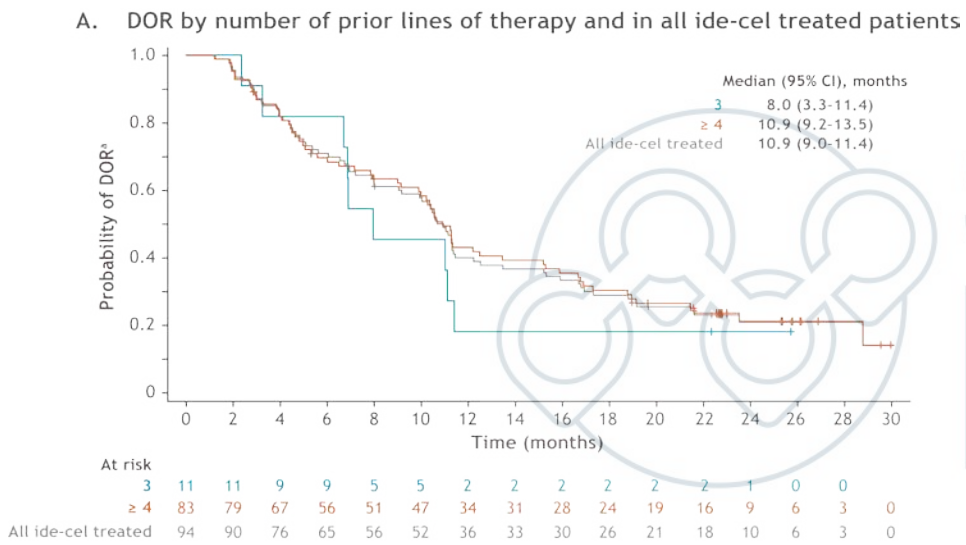


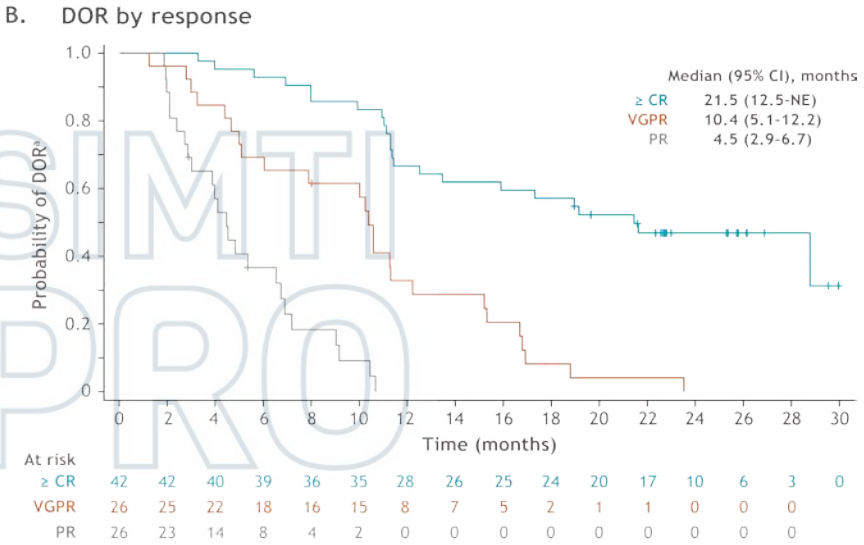
	Dose, × 10^6 CAR+ T cells			
	150 (n = 4)	**300 (n = 70)**	**450 (n = 54)**	**300-450 (n = 124)[c]**
ORR, n (%)	2 (50)	48 (69)	44 (81)	92 (74)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	41 (33)
Median DOR, mo[a,b]	–	9.9	11.3	10.9
Median PFS, mo[a,b]	–	5.8	12.2	8.8
Median OS, mo[a,b]	–	20.4	24.8	24.8

EP1009;

ORR, overall response rate; CRR, complete response rate

Duration of response





[a]DOR was measured from the start of first PR or better and is only applicable for patients with PR or better

DOR, duration of response; PR, partial response;
CR, complete response; VGPR, very good partial response

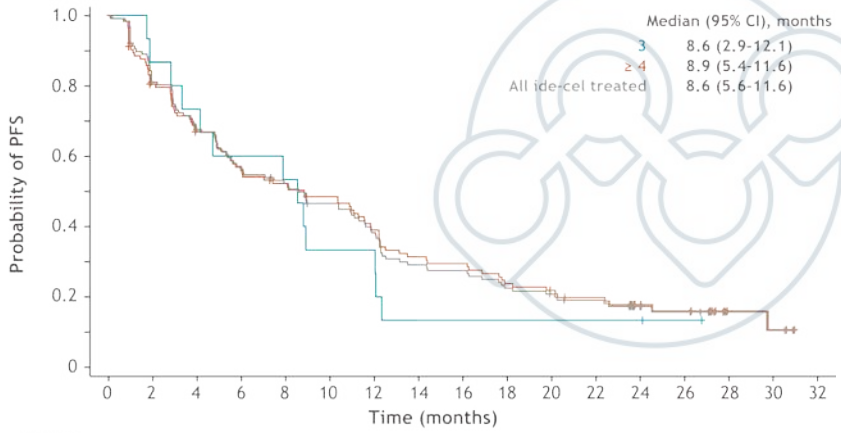
Provided by BMS in response to unsolicited requests only

Oriol et al, Poster Presentation: *EP1009;* EHA 2021

KarMMA-1 Study (Ide-cel) Long Term Follow-up Analysis

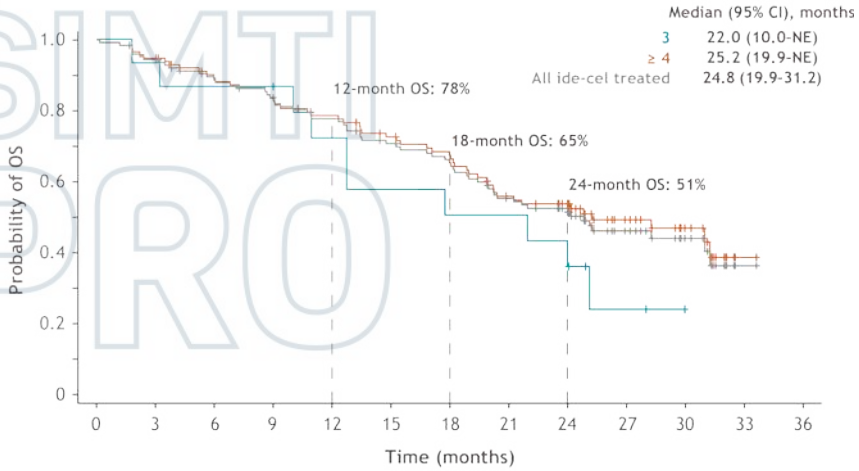
- Medium follow-up of 24.8 months. mPFS 8.6 months. mOS 24.8 mo.

PFS by number of prior lines of therapy and in all ide-cel treated patients



At risk																	
3	15	13	11	9	8	5	5	2	2	2	2	2	2	1	0	0	
≥ 4	113	89	73	62	56	51	41	33	31	25	22	19	10	9	3	2	0
All ide-cel treated	128	102	84	71	64	56	46	35	33	27	24	21	12	10	3	2	0

OS by number of prior lines of therapy and in all ide-cel treated patients



At risk													
3	15	14	13	13	10	8	7	7	5	2	0	0	
≥ 4	113	106	94	87	80	71	65	52	43	24	14	1	0
All ide-cel treated	128	120	107	100	90	79	72	59	48	26	14	1	0

Anderson L et al. ASCO 2021. Abstr 8016.

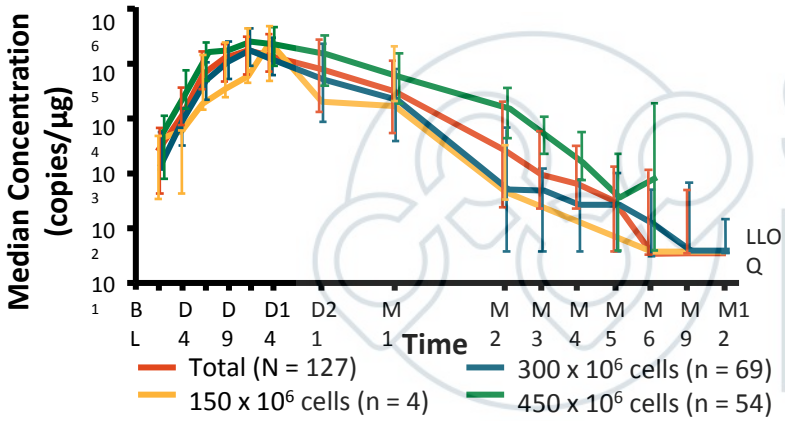
Ide-cel in elderly patients: durable responses consistent with the overall population

	Age ≥ 65 years (n = 45)	Age ≥ 70 years (n = 20)	All ide-cel treated (N = 128)
Age, median, years (range)	69 (65-78)	73 (70-78)	61 (33-78)
Prior antimyeloma regimens, median, n	6	5	6
Time since initial diagnosis, median, years	7	6	6
ORR (95% CI), n (%)	38 (84)	18 (90)	94 (73)
CRR (95% CI), n (%)	14 (31)	7 (35)	42 (33)[a]
PFS, median (95% CI), months	8.6 (4.9–12.2)	10.2 (3.1–12.3)	8.8 (5.6–11.6)
DOR,[a,b] median (95% CI), months	10.9	11.0	10.7
CRS,[c] n (%)			
Overall	40 (89)	20 (100)	107 (84)
Grade ≥ 3	2 (4)	2 (10)	7 (5)
NT,[d] n (%)			
Overall	11 (24)	6 (30)	23 (18)
Grade ≥ 3	4 (9)	1 (5)	4 (3)

[a] Includes CR and 1 sCR; [b] Among responders; [c] CRS was graded according to Lee criteria [Lee DW, et al. *Blood* 2014;124:188-195]; [d] NT was graded according to NCI CTCAE v4.03.
Berdeja JG, et al. Poster presentation at ASH 2020; abstract 1367.

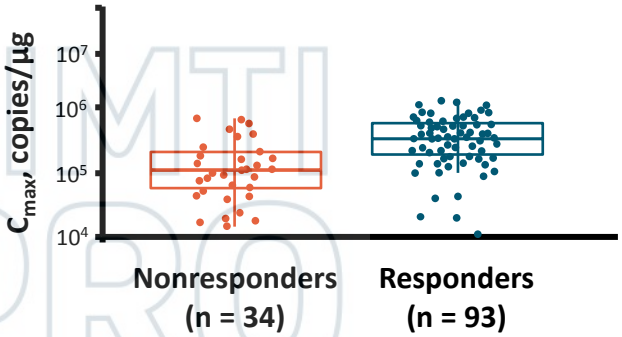
KarMMa: CAR T-Cell Parameters

CAR+ T-Cell Expansion and Persistence



	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Evaluable patients, n	118	100	49	27	11
Patients with detectable vector, n (%)	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)

Ide-cel Peak Exposure in Responders (≥ PR) vs Nonresponders (< PR)



- Median peak CAR+ T-cell expansion: 11 days
- **At higher target doses, median expansion increased**
- Higher peak exposure in responders vs nonresponders
- **Durable persistence noted up to 1 yr**

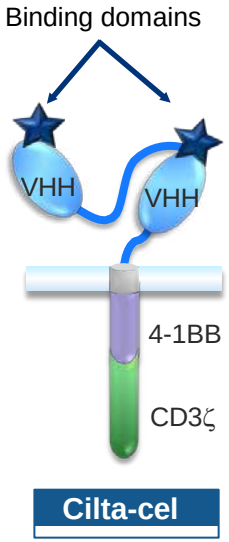
CAR, chimeric antigen receptor; ida-cel, idecabtagene vicleucel; MRD, measurable residual disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1. Munshi N, et al. ASCO 2020. Abstract 8503.

CARTITUDE-1: Phase 1/2 study of Cilta-Cel

CAR-T anti-BCMA (2 target)

Lentiviral vector-based + 4-1BB costimulatory domain; BCMA-catching domain **targets 2 different epitopes** simultaneously



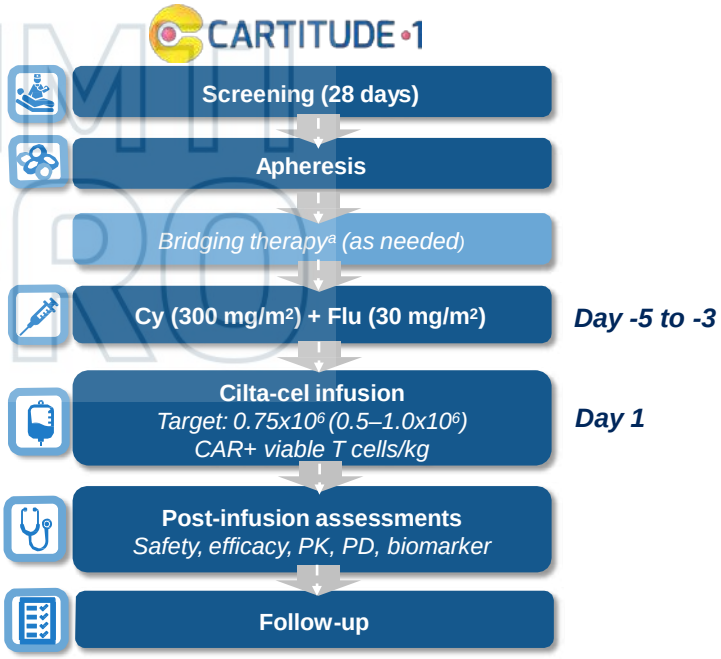
Primary objectives

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel by ORR

Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- **At least 3 prior lines of therapy, including PI, IMiD, and anti-CD38 or double-refractory**

- Median administered dose: 0.71×10^6 ($0.51–0.95 \times 10^6$) CAR+ viable T cells/kg



Median number of prior therapies: 6

CAR, chimeric antigen receptor; clita-cel, ciltacabtagene autoleucel; CD, cluster of differentiation; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance score; Flu, fludarabine; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall survival rate; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics.

1. Madduri D, et al. ASH 2020. Presentation 177.

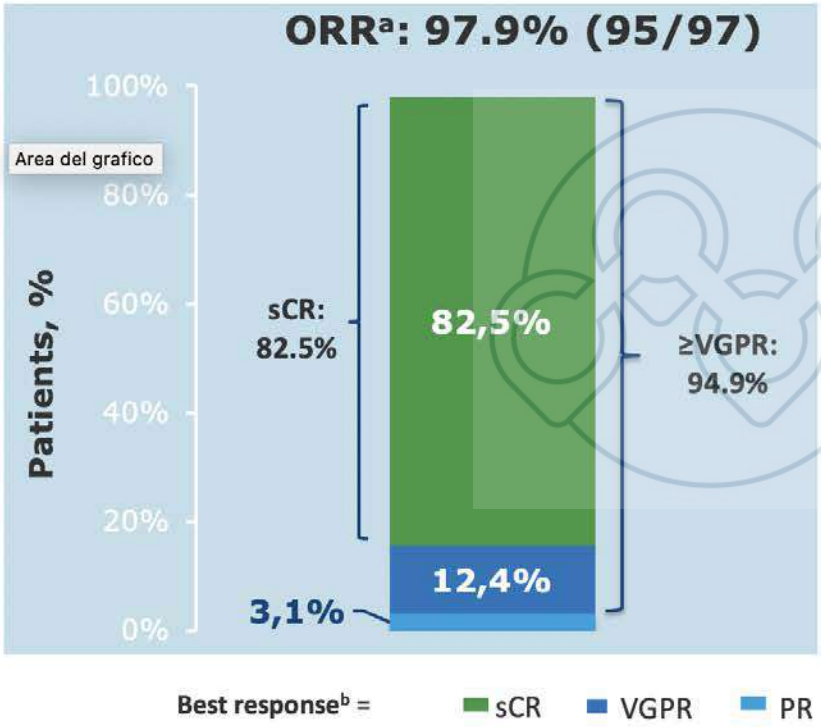
CARTITUDE-1: Demographics and Baseline Characteristics

Characteristics	N=97
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone marrow plasma cells ≥60%, n (%)	21 (21.9)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[a]

Characteristics	N=97
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[b] n (%)	97 (100)
Penta-drug exposed,[c] n (%)	81 (83.5)
Triple-class refractory[b]	85 (87.6)
Penta-drug refractory[c]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)
Years since diagnosis, median (range)	5.9 (1.6–18.2)

Thomas Martin et al., Oral Presentation abs. n. 549 Presented at the 63rd ASH; December 11-14, 2021; Atlanta, GA/Virtual

CARTITUDE-1: Efficacy Response



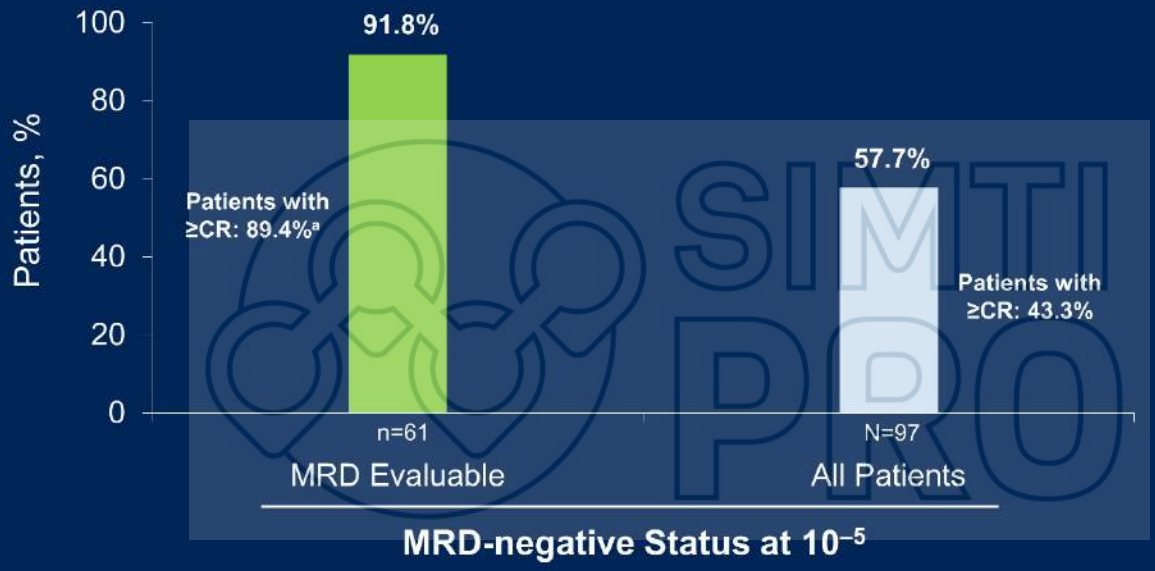
Responses deepened over time from the 1-year follow-up

Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)
- 60.5% of patients are still progression-free at 2 years

Thomas Martin et al., Oral Presentation abs. n. 549 Presented at the 63rd ASH; December 11-14, 2021; Atlanta, GA/Virtual

CARTITUDE-1: Minimal Residual Disease 10^{-5}

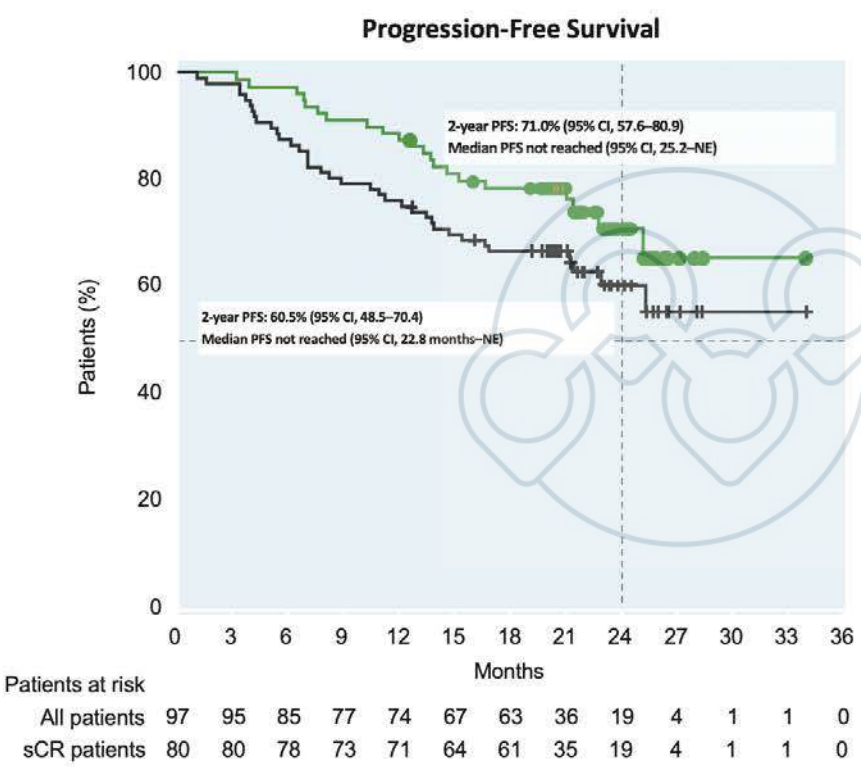


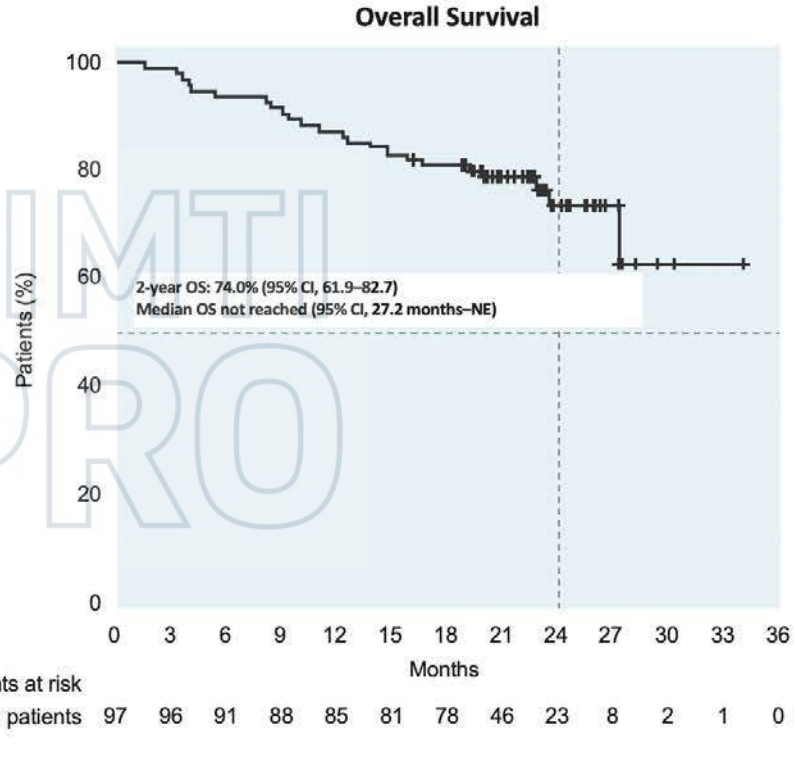
Almost all (91.8%) evaluable patients were MRD negative

Median time to MRD 10^{-5} negativity: 1 month (range, 0.8–7.7)

MRD, minimal residual disease; sCR, stringent complete response.
MRD was assessed in evaluable samples (ie, patients with identifiable clone at baseline and sufficient cells for testing at 10^{-5} threshold in post treatment samples) by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at Day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine. [a]Denominator n=47; evaluable MRD sample within 3 months of achieving CR/sCR until death/progression/subsequent therapy.

CARTITUDE-1: PFS and OS





All patients sCR patients

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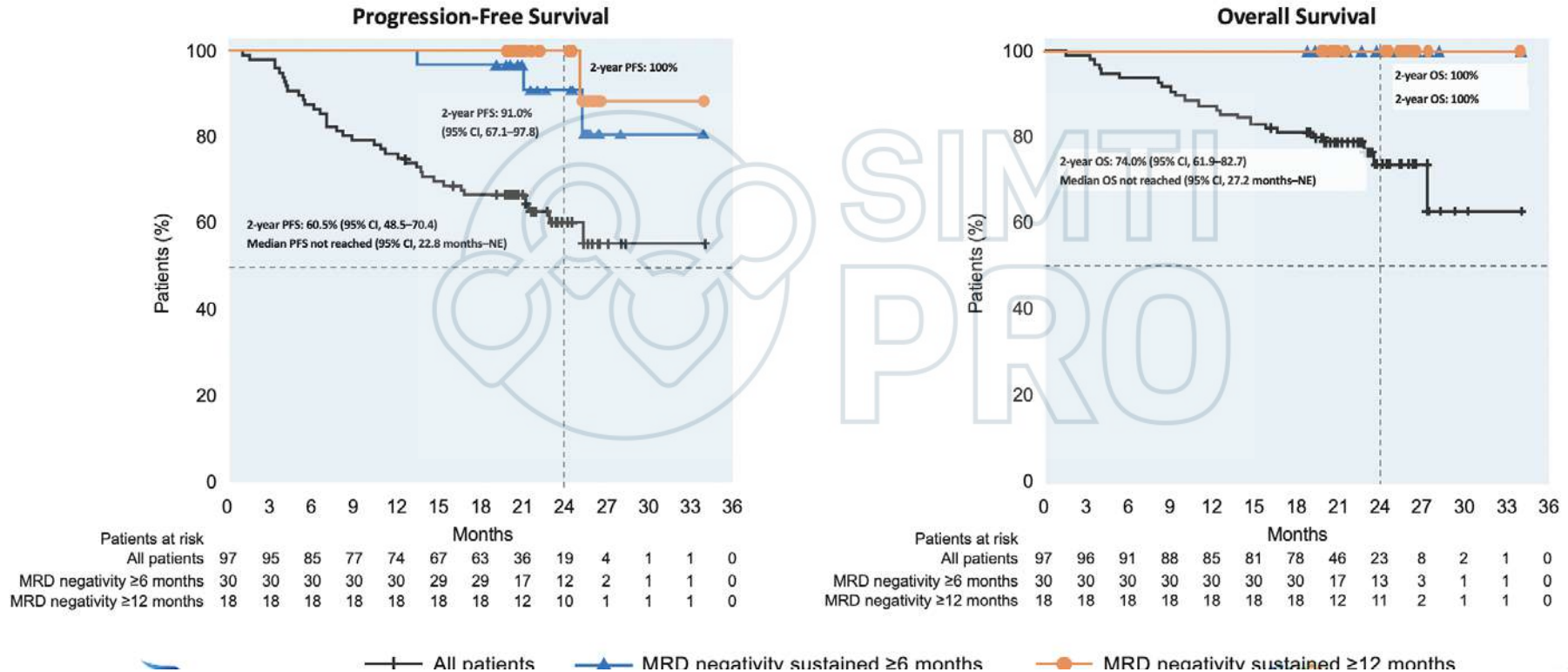
CARTITUDE-1: PFS and OS by MRD Negativity (10^{-5}) sustained for ≥ 6 and 12 months

✓ **Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})**



Thomas Martin et al., Oral Presentation abs. n. 549 Presented at the 63rd ASH; December 11-14, 2021; Atlanta, GA/Virtual

Cytokine release syndrome and neurotoxicity with anti-BCMA CAR-T

CRS	Ide-cel treated [1] (N = 128)
≥ 1 CRS event, n (%)	107 (84)
Max. grade, n (%)[a]	
1 or 2	100 (78)
≥ 3	7 (<5)
Median onset, days (range)	1 (1-12)
Median duration, days (range)	5 (1-63)
NT	
≥ 1 NT event, n (%)	23 (18)
Max. grade (CTCAE), n (%)[b]	
1 or 2	18 (14)
3	5 (4)[c]
Median onset, (range) days	2 (1-10)
Median duration, (range) days	3 (1-26)

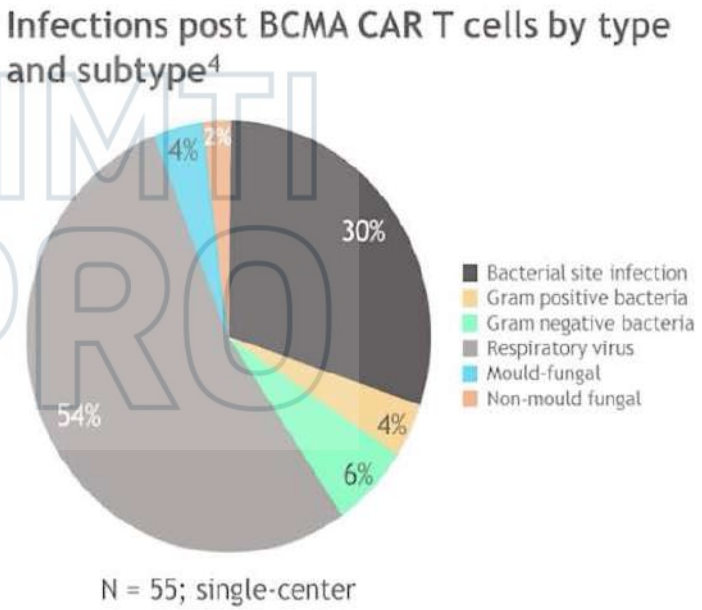
CRS	Cilta-cel treated[2] (N = 97)
≥ 1 CRS event, n (%)	92 (95)
Max. grade, n (%)[a]	
1 or 2	87 (90)
≥ 3	5 (5)
Median onset, days (range)	7 (5-8)
Median duration, days (range)	4 (3-6)*
NT	
≥ 1 NT event, n (%)	28 (29)
Max. grade, n (%)	
1 or 2	17 (17)
≥ 3	11 (11)
Median onset, (range) days	8 (6-8)[d] 27 (16-73)[e]
Median duration, (range) days	4 (3-7)

Oriol A, et al. Poster presented at EHA 2021; EP1009; Berdeja JG, et al. Lancet 2021;398:314-324

Cytopenia and infections with anti-BCMA CAR-T

Cilta-cel, %[1]	N = 97	
	Any grade	Grade ≥ 3
Neutropenia	96	95
Lymphopenia	53	50
Infection	58	20
Hypogammaglobulinaemia	NR	NR

Ide-cel, %[2,3]	N = 128	
	Any grade	Grade ≥ 3
Neutropenia	91	89
Lymphopenia	28	27
Infection	70	27
Hypogammaglobulinaemia	21	< 1



Ide-cel has obtained regulatory approval in the US, EU, and Japan. In the EU, ide-cel is indicated for RRMM after 3 or more prior lines of therapy. Prescribing information may vary depending on local approval in each country or region. Cilta-cel is an investigational therapy and is not approved by any regulatory agency.
The data presented are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
NR, not reported.

1. Berdeja JG, et al. *Lancet* 2021;398:314-324; 2. Munshi NC, et al. *N Engl J Med* 2021;348:705-716; 3. Anderson LD, et al. Poster presentation at ASCO 2021; abstract 8016; 4. Reproduced from Kambhampati S, et al. Blood Adv 2021;Sep 20. doi: 10.1182/bloodadvances.2020004079

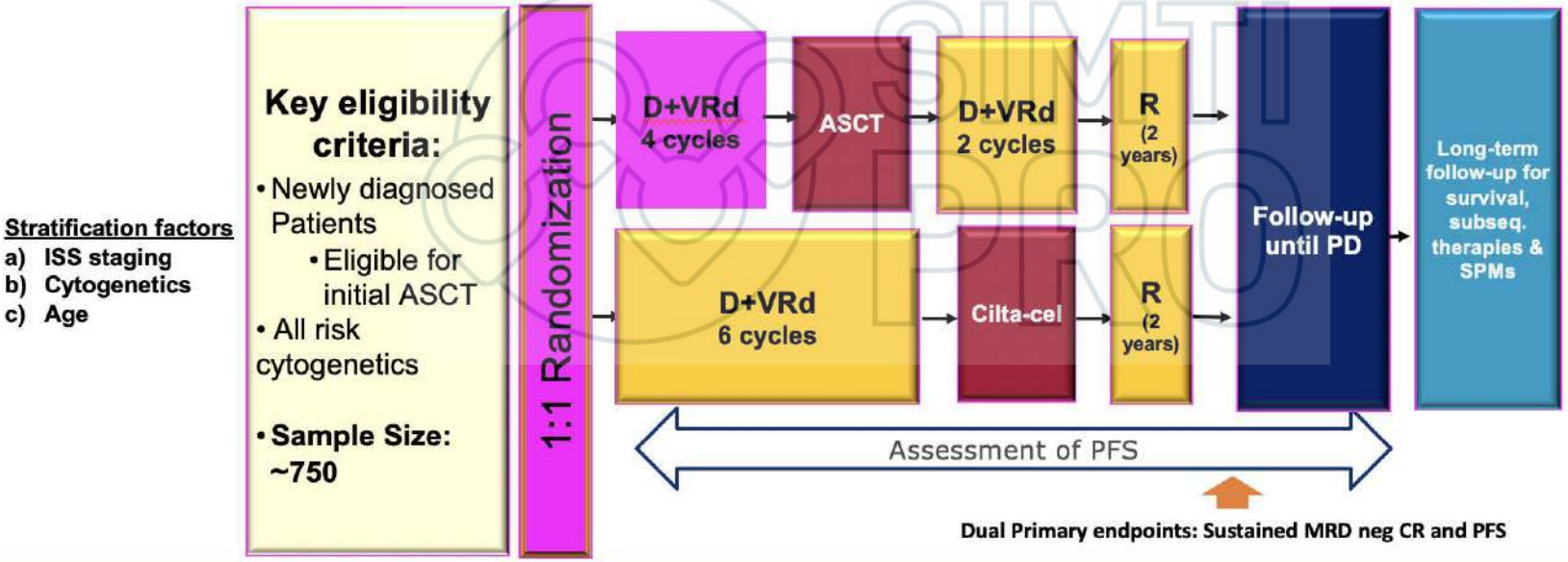
The future of CAR-T cell for MM

First-line	2° line	3° line	4° line
KarMMa-4: ide-cel in high-risk MM patients	KarMMa-2: ide-cel in triple-class exposed, high-risk, early relapse MM patients		
CARTITUDE-5: cilta-cel in NDMM ASCT-ineligible patients		KarMMa-3: ide-cel vs SOC triplet regimens in RRMM patients	
CARTITUDE-6/EMN28: cilta-cel in NDMM ASCT-eligible patients	CARTITUDE-4: cilta-cel vs SOC triplet regimens in RRMM patients		
CARTITUDE-2: cilta-cel in multiple cohorts			

CAR-T vs ASCT in NDMM patients
CARTITUDE-6/EMN28 randomized study

Dual primary endpoints:

Sustained MRD-neg CR and PFS



MRD (BM aspirate) time-points:

- Within 7 days prior to melphalan conditioning.
- After D+VRd consolidation, prior to initiating lenalidomide maintenance therapy.
- At time of suspected CR or sCR.
- After initial CR or sCR is confirmed, then once 3 months after, then every 6 months (+1 month) for 5y, then yearly until PD for participants that are in CR or sCR.

MRD by PET/CT (optional, if locally available): At time of BM MRD-negative CR and every 12 months in BM MRD-negative participants.

Dara, daratumumab; V, bortezomib; R, lenalidomide; d, dexamethasone; ASCT, autologous stem-cell transplantation; PFS, progression-free survival; MRD, minimal residual disease; CR, complete response; sCR, stringent complete response; ISS, International Staging System; SPM, second primary malignancy; PD, progressive disease; BM, bone marrow

Gay F et al. EMN22

Conclusions

- Anti-BCMA CAR-T ide-cel and cilta-cel showed, in heavily pre-trated patients, unprecedented results in terms of responses and PFS → up to 50% of patients alive and free from progression (and treatment) at 2 years

- Anti-BCMA CAR-T are likely to re-design the treatment landscape of RR as well as NDMM patients

- Despite the excellent results observed with ide-cel and cilta-cel no plateau in PFS and OS curve was observed

- Treatment with CAR-T must be optimized (use in earlier lines, better cytoreduction, enhanced CAR-T persistence, immunemostimulatory agents to complement their efficacy)

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